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Original

Emotional Evaluation of Pain in Migraine Patients

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Abstract : In the present study, we investigated how pain perception by migraine (MG) patients may differ from that of normal subjects. We simultaneously measured respiration and used an electroencephalogram to find inspiration-related (I-α) potentials during pain stimuli, which are usually observed in normal subjects during emotional arousal. There were no differences in pain threshold levels, maximum pain levels, scales of the level of pain, state, and trait anxiety, or respiratory rate during rest and stimulation between normal and MG subjects. When anticipating a pain stimulus, respiratory rate increased in both MG and normal subjects. However, I-α potentials were only found in normal subjects. We suggest that the absence of I-α potentials in MG patients may be due to the fact that pain-induced pervasive cortical excitability may not be sufficient to concentrate the brain rhythms to phase-lock. Hypersensitivity towards light, sound, and various sensations is often reported in MG. Thus, there may be a tendency in MG subjects to avoid concentrating on one external stimulus to protect against increased hypersensitivity. It may be that MG patients intuitively know that decentralizing their attention can avoid triggering an MG attack.

Key words : migraine, pain perception, respiration, electroencephalogram, inspiration-related potentials

Introduction

The past decade has seen considerable progress in migraine (MG) research ; however, the pathogenesis of this condition remains uncertain. MG is a complex disorder of the brain that involves multisensory disturbances. Symptoms of MG include a primary headache accompanied by disordered perceptions of light, sound, and smell[1]. Patients often complain of hypersensitivities towards normal light or sound that induce headache as well as nausea. It could be assumed that, in MG, higher perceptual sensitivities may be associated with altered pain perception in response to external stimuli than in normal subjects.

In the present study, we investigated how the pain perception of MG patients differs from

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that of normal subjects. To this end, we simultaneously measured respiration and used an electroencephalogram (EEG) to detect inspiration-related potentials during pain stimuli that are usually observed in normal subjects during emotional arousal.

Respiratory activity has been used to evaluate emotional levels in humans[2,3] and studies have shown that negative emotions, such as anxiety, increase respiratory rate[4]. This increase in respiratory rate is correlated with individual anxiety levels[4], suggesting that the same area in the brain may be responsible for respiratory changes and anxiety. In the present study, we used dipole analysis to find areas related to anxiety and to the increase in respiratory frequency[4]. If the subjective feeling of anxiety increases respiratory rate, electrical current sources synchronized with the onset of inspiration during anxiety are present in limbic areas[5]. From 350 to 400 ms after the onset of inspiration, a positive wave is observed in the averaged EEG activities triggered at the onset of inspiration. This positive wave is referred to as a respiration-related anxiety potential (RAP). These inspiration-related rhythmic oscillations are also observed in the averaged potentials triggered by the onset of inspiration during odor stimuli[6].

In the present study, we used this method to evaluate pain perception in normal controls and MG patients to determine whether the pain sensation of MG patients differs from that of normal subjects, as well as whether respiration-related potentials are observed in both normal subjects and MG patients during the perception of pain.

Methods

Eight MG patients (mean 34.3±12.8 years; three men and five women) and eight age-matched healthy, normal subjects (mean 29.0±3.2, years; all men) participated in the present study. None of the patients was receiving drug treatment. Patients had been diagnosed with MG according to the International Classification of Headache Disorders (ICHD II) criteria (code 1.1)[7]. EEGs were recorded in MG patients during the inter-critical phase, at least 72 h after the last attack. All subjects provided informed consent and the study was approved by the Ethics Committee of the Showa University School of Medicine.

Because emotions induced by painful stimuli may be influenced by individual anxiety levels, anxiety levels were evaluated in all subjects in the present study using Spielberger's State-Trait Anxiety Inventory (STAI)[8]. MG patients and normal subjects were examined using the protocols described below under the same environmental conditions.

Measurement of inspiration-related potentials

The method for observing inspiration-related potentials has been described in detail by Masaoka *et al*[5,6]. Subjects were informed that electrical pain stimulation would be delivered through a needle attached to the dorsum of their left hand (see below) at certain times during the experiment; the time elapsed while waiting for the electrical stimuli is referred to as "anticipatory anxiety". During the experiment, EEG and respiration rate

were recorded simultaneously.

RAP and inspiration phase-locked α-band oscillations (I-α)[6] are the inspiration-related potentials observed in the averaged potentials triggered by the onset of inspiration by emotional and olfactory stimuli. RAP and I-α are observed when emotional and respiratory changes occur simultaneously in an emotional situation. This is based on the assumption that if the onset of changes in inspiration in response to certain emotions is used to average the EEG, respiration-related potentials will be observed.

Pain stimuli

Before the experiment, MG and normal subjects were tested for their threshold level of pain, defined as the level at which the stimulation is small but can be felt, and pain level, defined as the level at which the stimulation is painful but can be endured.

Electrical stimuli were delivered according to the method described by Inui *et al*[9]. The cathode consisted of a plastic plate, a soft stop device, and a stainless steel needle (0.5 mm in diameter). The soft stop device protruded 1.0 mm from the plate and, in turn, the tip of the needle protruded 0.2 mm from the soft stop device. By pressing the electrode plate against the skin gently, the needle tip was inserted adjacent to the nerve endings of the thin myelinated fibers in the epidermis and superficial part of the dermis. As the anode, a surface electrode (1.0 cm in diameter) was placed on the skin 4 cm from the needle electrode. Stimulation produced a well-defined pricking pain without definite tactile sensation. The needle was set on the dorsum of the left hand between the first and second metacarpal bones. Stimuli were delivered from an isolator connected to the electrical device (Nihon Kohden, Tokyo, Japan).

MG and normal subjects were instructed to rate their pain intensity and pain-induced unpleasantness on a visual analogue scale (VAS) ranging from 0% (no pain at all) to 100% (worst pain imaginable). After determination of the threshold level of pain and pain levels, subjects were asked to indicate their pain level using the VAS. VAS ratings were also obtained after each of the experiments described in the following sections.

Measurement of EEG and respiration

Nineteen electrodes were attached to the scalp according to the International 10-20 system, with the reference electrode on the right earlobe. EEGs and electro-oculograms were recorded and stored in a digital EEG analyzer (DAE-2100; Nihon Kohden). The EEGs were sampled at 500 Hz through a 0.016–30-Hz bandpass filter. Impedances were kept below 10 kΩ. Respiratory flow data, measured with a respiratory flow monitor (Minato, Osaka, Japan), were also stored in the EEG analyzer. Inspirations were flows downward from the 0 level, whereas expirations were flows upward. The onset of inspiration (onset of flow going downward from 0) was used as a trigger for averaging potentials. All sniffing activities were excluded from averaging to avoid the effects of artifacts caused by mechani-

Table 1 Comparisons pain perceptions, anxiety and respiratory rate between normal subjects and MG

	Normal subjects (N＝8)	MG (N＝8)
Age (years)	29±3.2	34.3±12.8
Pain threshold level (mv)	0.11±0.05	0.11±0.06
Maximum Pain level (mv)	0.9±0.7	0.93±0.7
VAS for painfulness (%)	63.5±8.6	69.9±25.5
STATE	42±10.4	43.5±11
TRAIT	47.2±10.8 *	47.3±10.4 *
Respiratory rate (rest)	13.6±2.7 *	14±3.7 *
Respiratory rate (stimuli)	16.1±2.7	17.9±4.3

* $P < 0.05$

cal movement of the mandibular muscles on EEG activity. Eyeblinks or artifactual activity exceeding ±50 μV were also excluded.

Potentials were averaged by the EEG analyzer during the time that elapsed while waiting for the electrical pain stimulus (number of averaging, mean 50.5±3.5 for each trial).

Power analysis of EEG bands

The EEG power of the band component for each electrode position was calculated from the inspiration-triggered averaged potential for each subject. Power was calculated over 500 ms of averaged data. Spectral power was analyzed by fast Fourier transformation (spectral analysis) using EEG-analysis software (EEG Focus, Version 2.1 ; Nihon Kohden).

Statistical analysis

All statistical analyses were performed using a commercially available statistical package (SPSS Version 11.0 ; SPSS, Tokyo, Japan). Comparisons of age, pain threshold level, maximum pain levels, STAI scores, and respiratory rate during rest and pain between MG and control subjects were made using Wilcoxon's signed-rank test. Power spectra of the average potentials of each electrode were compared between MG and control subjects using one-way repeated-measures analysis of variance (ANOVA). $P < 0.05$ was considered significant. The mean power spectra of electrode band components calculated from averaged potentials were compared between MG and normal subjects using Wilcoxon's signed-rank test.

Results

Pain threshold level, maximum pain level, VAS for levels of pain, state, and trait anxiety, and respiratory rate during rest and pain stimuli are given in Table 1. There were no significant differences in any of these variables between normal and MG subjects.

Grand-average EEGs from 19 electrodes triggered by the onset of inspiration are shown

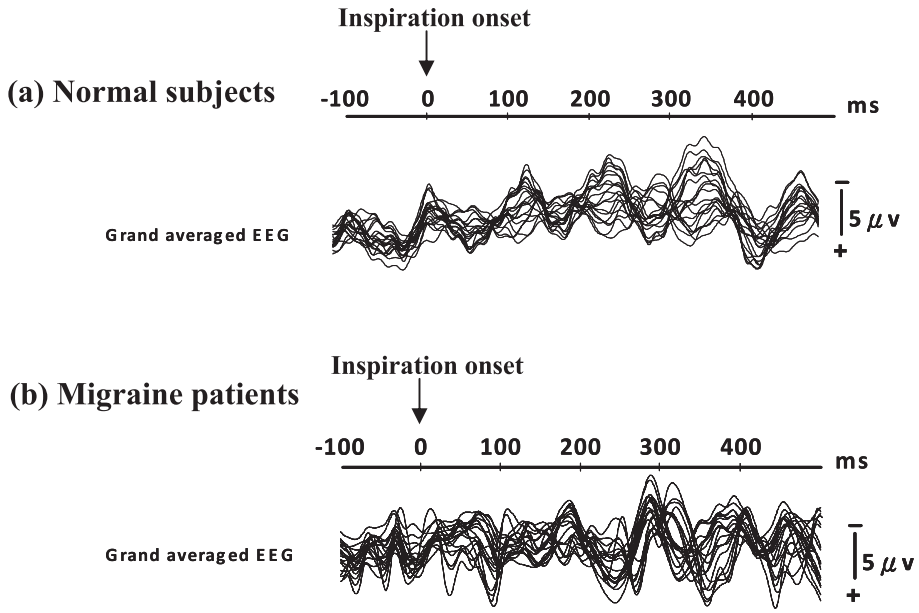

Fig. 1. Grand-average electroencephalograms (EEGs) from 19 electrodes triggered by the onset of inspiration in (a) normal subjects and (b) migraine (MG) patients.

in Fig. 1. The α-rhythm is a waveform with a characteristic 9–12 Hz frequency. As can be seen in Fig. 1, the waveforms had an α-band oscillation that was phase-locked to inspiration, I-α. These waveforms were not observed during the expiratory phase.

The mean power spectra of electrode band components calculated from averaged potentials during all trials are shown in Fig. 2. For each electrode, the powers of the 9–12 Hz (α) bands were higher in Fp2, Fp2, F3, F4, T5, T6 Fz, Cz, and Pz in normal compared with MG subjects (Fig. 2).

Discussion

In the present study, we sought to identify differences in the perception of pain stimuli between normal subjects and MG patients. Three approaches were used to identify any differences: (i) we compared pain threshold levels, maximum pain levels, and VAS scoring of pain between normal and MG subjects; (ii) we evaluated respiratory rate during anticipatory anxiety; and (iii) we looked for inspiration-related potentials in normal subjects and MG patients.

Pain perception in MG

There were no significant differences in pain threshold levels, maximum pain levels, and VAS scoring of pain between normal and MG subjects. These findings are in agreement with those of Gierse-Plogmeier *et al*, who reported that there were no significant differences

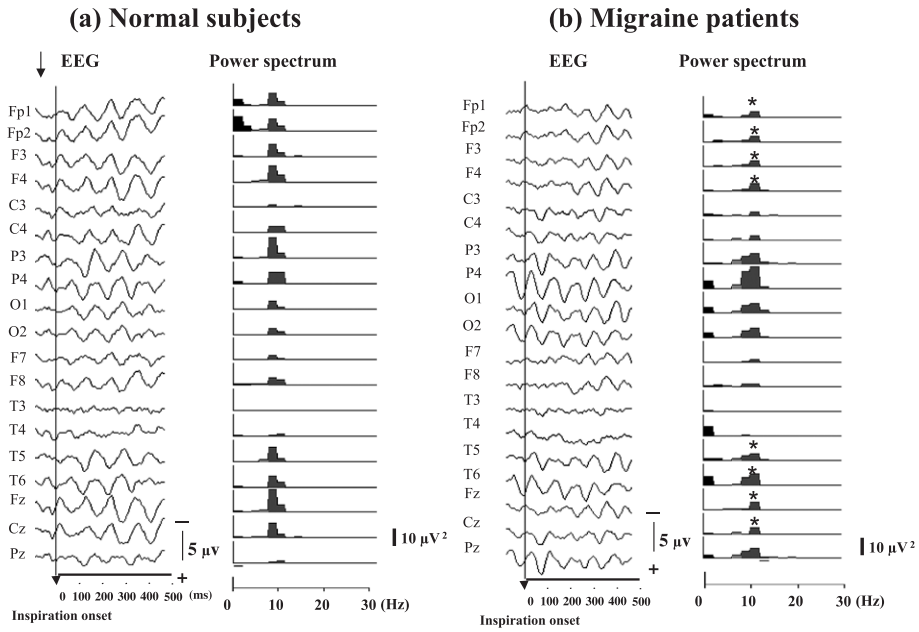

Fig. 2. Mean power spectra of electrode band components calculated from averaged potentials during all trials in (a) normal subjects and (b) migraine (MG) patients. For each electrode, the powers of the 9–12 Hz (α) band were higher in normal than MG subjects for Fp2, Fp2, F3, F4, T5, T6 Fz, Cz, and Pz. $^{*}P < 0.05$.

in these parameters between MG and normal subjects following peripheral stimulation[10]. In the present study, we only tested peripheral electrical stimuli; however, the trigeminal pain perception of MG patients has been reported to differ from that of normal subjects[10], with pain facilitation observed in trigeminal pain perception in MG patients. This difference in pain thresholds may be based on a lower density of nociceptors in peripheral regions compared with trigeminal regions of the body. In addition, the repetitive facial and head pain in MG patients during regular MG attacks can lead to a facilitation of all painful trigeminal stimuli. The lack of any difference between MG and normal subjects in all parameters evaluated in the present study following peripheral pain stimulation suggests that the perception of peripheral pain is independent of the pain-facilitation phenomenon observed for trigeminal areas.

Respiratory rate

Respiratory rate increased in both MG and normal subjects while anticipating the painful stimuli. In the present study, respiratory rate increased because of two factors: (i) pain; and (ii) the anticipation of a painful stimulus. Unpleasant emotions are associated with rapid and shallow breathing[6]. It has been reported that anticipatory anxiety increases respiratory rate[4] and that this increase in respiratory rate is associated with amygdala activity[5]. In the present study, negative emotions associated with the painful stimulus itself and antici-

patory anxiety contributed to the increase in respiratory rate in MG and normal subjects.

It has been suggested that the respiratory response can be used as an emotional index[3]. Based on this assumption, the respiratory responses observed in the present study are considered to be on the same level as emotions originating in the limbic system. In the present study, differences in respiratory-related potentials were observed between MG and normal subjects (see below).

Inspiration-related potentials

Inspiration-related potentials are observed when emotions occur with respiratory changes, such as the anxiety and emotional changes caused by odor stimuli[4, 6]. In the present study, we confirmed inspiration-related potentials categorized as 9–12 Hz, which were defined as I-α, in normal subjects (Fig. 1a). As can be seen in the power spectra shown in Fig. 2, for most of the electrodes (except C3, C4, T3, and T4), the power of 9–12 Hz was high in normal subjects. However, there was no rhythmic oscillation triggered by the onset of inspiration in MG patients (Fig. 2b). In MG patients, the power of the α-rhythm was low in the frontal areas (Fp1, Fp2, F3, F4, and Fz), the temporal areas (T5 and T6), and the parietal areas (Cz and Pz). Not all electrodes were synchronized with the onset of inspiration in MG subjects.

It has been reported that inspiration-related α-band oscillation is observed during odor stimuli[6], with the same study reporting that the synchronization of low-frequency cortical oscillations was generated from the basal forebrain, in areas related to the limbic system. α-Rhythms in the awake state could involve a large number of events, but the pattern of cortical and thalamic activities could be sensitive to respiratory rhythmic input, such that cortical rhythms tend to phase-lock to respiratory changes coexisting with emotional changes. In MG patients, I-α was not observed and this may be due to one of two factors: (i) the weak activation of the limbic system may not have been sufficient to synchronize all cortical rhythms from the limbic rhythm[11]; and (ii) cortical rhythms are difficult to phase-lock because of the cortical hyperexcitability that often characterizes MG patients[12]. As mentioned earlier, we assumed that there were no significant differences in arousal levels (emotional) and the limbic system between MG patients and normal subjects. Thus, we suggest that the absence of I-α in MG patients is due to the cortical hyperexcitability in these subjects. That is, pervasive cortical excitability induced by pain stimuli may not be sufficient to concentrate the brain rhythms to phase-lock. Brain rhythms consist of several types of oscillation generated in interacting cortical and thalamic neuronal networks[13]. If all cortical rhythms exhibit hyperexcitability in response to environmental stimuli, it could be difficult for potentials to synchronize, especially using inspiration as the trigger signal.

Respiration is greatly influenced not only by emotions, but also by various sensory stimuli. Although in the present study the VAS scoring of pain and pain perception were the same in MG and normal subjects, various other sensory processes may be involved in MG. For

example, hypersensitivity towards light, sound, and various sensations are often reported in MG[14]. In addition, there may be a tendency for MG patients to avoid concentrating on one external stimulus to avoid increased hypersensitivity to this one stimulus. It may be that MG patients intuitively know that decentralizing their attention can avoid triggering an MG attack.

We did not test the brain areas related to the potentials observed in the present study; however, the I-α of normal subjects induced by the anticipation of pain may be related to the limbic areas, specifically the amygdala, the emotion center. We speculate that these I-α are not observed in MG patients because many areas may be activated at the same time, which may inhibit activation of the limbic system[1, 2]. This possibility may be worth investigating in future studies.

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